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UNTOWARD REACTIONS TO LYSERGIC ACID DIETHYLAMIDE (LSD) RESULTING IN HOSPITALIZATION*

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MOST typically, medical research has proceeded from clinical observation to clinical investigation to laboratory experiment. Some of the striking exceptions to this pattern have been studies of a variety of pharmacologic agents that are capable of producing changes in psychic state. These drugs, first isolated or synthesized in the laboratory, occasionally create a new clinical syndrome or a new etiology of an old syndrome as an undesirable by-product of individual abuse or poor judgment by the physician.

A sudden surge of admissions to the Bellevue Psychiatric Division after ingestion of d-lysergic acid diethylamide (LSD) prompted us to review the history of its discovery and use. In 1938 Stoll and Hofmann,¹ of the Sandoz Research Laboratories, succeeded in synthesizing this compound along with a number of related alkaloids of the ergonovine type. However, it was not until April, 1943, that Hofmann,² following the path of the Prince of Serendip, discovered the hallucinogenic properties of this substance. These were then confirmed in a now classic case of self-experimentation. A series of careful experiments by Stoll³ showed that doses of about 30 microgm. of LSD administered by mouth to nonpsychotic subjects produced autonomic changes, predominantly sympathomimetic, kaleidoscopic visual hallucinations, with intense and varying coloring, hyperacusis, synesthesia, tactile paresthesia, illusions, distortions of body image, feelings of estrangement and depersonalization and disturbances of mood. These occurred in the presence of unaltered orientation, critical self-judgment and the ability to respond to interrogations by the observer. Particularly striking was the minute amount of LSD required to produce such changes. Although individuals differ in degree of sensitivity to the action

of this agent the intensity of the effects is proportional to the dose. Tolerance develops rapidly to repeated daily doses and disappears completely three days after the medication is discontinued.

In the 1950's LSD and other "hallucinogenic" compounds were studied extensively because they were thought to produce symptoms mimicking schizophrenia.⁴ It is now clear that there are significant differences: the spectacular visual illusory phenomena and perceptual distortions induced by the hallucinogenic compounds are not typical of schizophrenia. However, the depersonalization, which some nonpsychotic subjects display under the influence of higher doses of these drugs, is strikingly similar to what may be seen in acute schizophrenic reactions. Experimental catatonia has produced in animals when relatively large doses have been administered.⁵

Despite stereotyped aspects of the response, subjective experiences vary widely. They appear to be related to the previous personality of the subject and the setting of the experience.⁶ Some subjects describe the drug experience as frightening and believe that they have passed through a "living hell"; others describe their thoughts, hallucinations and sensations of depersonalization in rapturous terms.

The drug has been used widely on volunteer subjects and, more recently, in therapeutic settings. In many of these studies it was noted that in occasional subjects overwhelming anxiety of panic proportions required interruption of the experimental situation.⁷ This panic usually was rapidly alleviated by the administration of barbiturates or phenothiazines. Occasional prolonged psychotic episodes have been described.⁷ These occurred despite elimination from the experiment of psychotic or paranoid personalities or people prone to the excessive use of denial and despite the subject's awareness of the presence of external control in the person of the experimenter, who approved of his taking the drug. As Kluver⁸ points out, "We are undoubtedly safe in assuming that the hallucinations in a mescalized person dictating a description of his visual descriptions experiences to an assistant are in some ways not the same as of a person with mescal

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psychosis." He refers to a man under the influence of mescaline who was found crawling about the floor with extreme care, but who averred that he was a fly walking on the ceiling upside down and that if he moved quickly he would fall down and be injured. This is in striking contrast to the geometric images typically described after ingestion of mescal.

In 1963 psychiatric complications that followed the unsupervised use of LSD were first reported, and 9 cases were described.⁹ In New York City there has recently been an increase in the unsupervised use of these compounds, stimulated in part, perhaps, by the laudatory descriptions of Huxley¹⁰ and Leary, Metzner and Alpert,¹¹ who have emphasized the "consciousness-expanding" properties of the drugs. The number of patients admitted to the hospital as a result of taking the drug as it has become more freely available in the community has also increased.

CLINICAL DATA

In the four-month period from March through June, 27 patients were admitted to the hospital as a consequence of ingestion of LSD. The first 12 cases were extensively worked up and are presented below.

The patients had certain characteristics in common. All but 1 were in their twenties. Most had attended college, but only 2 had graduated. Their employment record was good, but only 2 were working in a professional or executive capacity. None were on welfare although a few were supported by parents or paramours. Most were deeply concerned with philosophical questions and particularly interested in Zen Buddhism and Yoga. All had some degree of personality difficulty before taking the drug; 5 were definitely psychotic before their LSD experience. With the exception of the patient over thirty they had been experimenting with different drugs such as barbiturates, amphetamine, alcohol and marijuana in an effort to alleviate anxiety. LSD appeared to offer a new hope to them because it promised more than narcotization; they believed that in the height of the experience new understanding would be found. Ready availability of the drug facilitated self-administration, usually in doses of 200 to 400 microgm.

The syndromes appear to fall into the three somewhat overlapping types: panic reaction; reappearance of "drug" symptoms without reingestion of the drug; and overt psychosis. There were 7 panic reactions, 3 cases of reappearance, and 3 of overt psychosis. One of the patients had a panic reaction and one month later returned with a recurrence of symptoms although he had not taken additional LSD.

Panic Reactions

Panic is often seen at some stage of the LSD ex-

perience. However, it rarely leads to hospitalization despite the many people now taking the drug without adequate supervision. Of this group of patients 4 took the drug alone in their apartments and came to the hospital seeking relief from their terror. Another 2 were brought in by friends who thought that they could not control the patient or prevent him from hurting himself. The seventh, admitted after he fell from an open window, was acting as a guide for a friend undergoing his first exposure to LSD.

Two of the group were classified as schizophrenic although neither showed secondary manifestations. Three others functioned at a borderline level and were considered to be schizoid personalities. The remaining 2 were diagnosed as having personality disorders. The 7 patients had some personality characteristics in common, for they were overly ideational, obsessive, constricted, and stereotyped in responses to people and new situations. There were no gross sensorial disturbances on admission or subsequently although recollection of many details of the LSD experience was hazy. Recovery was rapid, and all were discharged from the hospital within one to three days.

A typical patient with a panic reaction is presented as Case 1:

CASE 1. A 21-year-old woman was admitted to the hospital along with her lover. He had had a number of LSD experiences and had convinced her to take it to make her less constrained sexually. About half an hour after ingestion of approximately 200 microgm., she noticed that the bricks in the wall began to go in and out and that light affected her strangely. She became frightened when she realized that she was unable to distinguish her body from the chair she was sitting on or from her lover's body. Her fear became more marked after she thought that she would not get back into herself. At the time of admission she was hyperactive and laughed inappropriately. Stream of talk was illogical and affect labile. Two days later, this reaction had ceased. However, she was still afraid of the drug and convinced that she would not take it again because of her frightening experience.

Reappearance of Symptoms

Three patients had recurrent experiences after they had stopped taking LSD. For 2 there was an interval of one or two months between the taking of the drug and the re-experiencing of depersonalization and perceptual distortions. Both patients had been on the drug for a limited time and had had relatively few exposures (9 to 15).

This was in marked contrast to the third patient (Case 2), who had had over 200 exposures in a period encompassing many years. Although he had not ingested any drug for over a year before admission, he reported many transient episodes of catatonia and visual hallucinations that were similar to his behavior under the immediate influence of LSD.

All 3 men were preoccupied with the effect of LSD upon them and thought of it often. They correlated the return of symptoms with stress or

anxiety. Diagnostically, 2 of the patients were considered to have chronic schizophrenia. The third patient (Case 3) was classified as borderline rather than overtly psychotic although projective testing recorded a thinking disorder consistent with the diagnosis of schizophrenia.

CASE 2. A 25-year-old man was taken to Bellevue Hospital by acquaintances who had noted that he was wandering vacantly and aimlessly at work and was relatively uncommunicative.

Despite a somewhat withdrawn childhood no major difficulties were encountered until his senior year in high school, when he became involved with "beatniks" and took mescaline, amphetamine and marijuana. His college work was interrupted by service in the armed forces, from which he received a medical discharge. After returning to college, he became involved in experiments with hallucinogenic drugs, which led to multiple exposures. In addition he described participation in a chaotic communal life that was followed by termination of his marriage. After he left the group his life continued to be disorganized. He became involved in Buddhism and stopped taking LSD or other drugs. Despite the fact that he apparently had not used these agents for the past year, he experienced the incommunicable "oneness and suchness" that he had previously experienced after LSD, described as, "what you realize before you realize that there are other beings in the world whose range is as profound as or more profound than your own." He continued to experience repeated visual hallucinations and catatonic episodes, similar to those described while he was taking LSD.

After one month in the hospital he remained constricted, concrete and illogical. There was the persistent use of highly convoluted, inappropriate abstractions.

CASE 3. A man in his late twenties came to the admitting office in a state of panic. Although he had not taken any drug in approximately 2 months he was beginning to re-experience some of the illusory phenomena, perceptual distortions and the feeling of union with things around him that had previously occurred only under the influence of LSD. In addition, his wife had told him that he was beginning to "talk crazy," and he had become frightened. Despite a somewhat disturbed childhood and an interrupted college career he had carefully controlled his anxiety by a rigid obsessive-compulsive character structure, which had permitted him to work with reasonable success as a junior executive. Although for 6 years before admission he had felt the urge to seek help and self-understanding, he had never sought psychiatric care. He had tried marijuana, peyote and finally ground morning-glory seeds. Most of his 15 experiences with LSD had been pleasurable although he also had had 2 panic reactions, neither of which had led to hospital admission. On these occasions he thought that he was losing control and that his whole body was disappearing. At the time of admission he was concerned lest LSD have some permanent effect upon him. He wished reassurance so that he could take it again. His symptoms have subsided but tend to reappear in anxiety-provoking situations.

Extended Psychosis

The 3 patients in whom an extended psychosis followed a single ingestion of LSD clearly had long standing schizophrenia. They had experimented widely with other drugs before taking LSD, and considered the recent experience to be more vivid and of greater personal significance than anything they had previously known. Each anticipated greater self-understanding as an aftermath of the LSD ingestion and, indeed, did have profound personality alterations afterward. In the course of their experience they sought for perceptions and ideas

that would be tangible evidence that their hopes had materialized. In the isolation of the transcendental state they believed that they had achieved a resolution of their problems. Any feeling of terror that might have been present was rapidly replaced by a feeling of ecstasy as they felt they had achieved a new self.

As the effects of the drug wore off, these 3 patients were faced with the problem of returning to the real world and accommodating a vague, new self image, achieved under the influence of the drug, to reality. Conflict arose as they began to interact with other people and had to become reconciled to the fact that their new understanding was not readily grasped or responded to by others. Rather than give up their new-found, fictional sense of self, the psychotic patients strove to maintain their sense of uniqueness and withdrew from the world. At the time of admission 2 were catatonic, and the third, who had catatonic features, was markedly paranoid. After a month in the hospital 2 patients were discharged, whereas the third (Case 4) had to be transferred to another hospital for prolonged treatment:

CASE 4. A 23-year-old man was admitted to the hospital after he stood uncertain whether to plunge an upraised knife into his friend's back. His wife, an intelligent, nonpsychotic but masochistic woman, reported that he had been acting strangely since taking LSD approximately 3 weeks before admission. He was indecisive and often mute and shunned physical contact with her. On admission he was catatonic, mute and echopractic. He appeared to be preoccupied with auditory hallucinations of God's voice and thought he had achieved a condition of "all mind." On transfer to another hospital 1 month after admission, there was minimal improvement.

During his adolescence the patient had alternated between acceptance of and rebellion against his mother's religiosity and warnings of the perils of sex and immorality. He had left college during his 1st year after excessive use of amphetamines. He attended, but did not complete, art school. His marriage of 3 years had been marked by conflict and concern about his masculinity. Increasing puzzlement about the meaning of life, his role in the universe and other cosmic problems led to his ingestion of LSD. Shortly after ingestion he was ecstatic and wrote to a friend, "We have found the peace, which is life's river which flows into the sea of Eternity." Soon afterward, in a brief essay, he showed some awareness of his developing psychosis, writing, "I am misunderstood, I cried, and was handed a complete list of my personality traits, habits, goals, and ideals, etc. I know myself now, I said in relief, and spent the rest of my life in happy cares asylum. AMEN."

DISCUSSION

The popularity of LSD among the lay public has grown rapidly because of the belief that it expands consciousness and alters personality for the better. Although many high-school and college students take the drug ostensibly for "kicks" a large number of anxiety-ridden people have begun to experiment with it in the hope of achieving help. Most often, these people have taken hypnotics, stimulants and opiates before turning to LSD. As its popularity and availability increases, it is likely that people will turn to it before other drugs since LSD is believed

to offer relief with understanding, making it possible to achieve a sustained state of improvement.

In the patients whom we have extensively examined there has been no evidence of personality change for the better. Instead in 3 prolonged psychoses developed after a single or second ingestion of LSD. None improved markedly after one month in the hospital although 2 were able to be discharged. In 3 others deterioration of personality followed multiple ingestion. This was most noticeable in periods of stress, when it was necessary for them to mobilize their resources to counter anxiety. Instead of functioning effectively, they experienced depersonalization and a return of visual hallucinations, and were much more incapacitated than they had been before the LSD experience. The phenomenon of return of symptoms is not understood. Among the suggested explanations, which encompass both physiologic and psychologic processes, are permanent brain damage, gradual release of stored metabolite or drug, conditioned response and learned reaction to anxiety.¹²

Most of the patients were aware that possible dangers existed before they took the drug. Some carried their sugar cubes saturated with LSD with them for several months before acquiring sufficient courage to swallow it. All the patients discounted the likelihood of danger occurring, especially since they believed they were in a proper frame of mind to achieve benefit and made their surroundings as conducive to success as they could.

Although the possible dangers associated with the taking of LSD are mentioned in the popular literature about the drug¹³ they can be readily minimized by someone intent on obtaining the more highly touted positive effects, especially since any resultant psychosis is pictured as readily reversible and a step toward health. A central metaphor, which Leary¹⁴ employs to prepare the reader for a better understanding of the psychedelic effect, is as follows: "... it becomes necessary for us to go out of our minds in order to use our heads." He blames naïve and misinformed doctors for perpetuating an unfavorable LSD experience by treating it as if it were a real psychosis.¹⁵ In this context it should be recalled that the 3 patients who became psychotic after ingestion of LSD were first treated by their friends (with additional LSD in 1 case) and hospitalized only after they failed to respond to their ministrations. The friends, who were aware of prevailing attitudes in the popular literature, were contemptuous of the hospital staff and the possibility of rehabilitation through psychiatric efforts.

In the uncontrolled setting in which LSD is used in the community the danger of bodily injury also exists since a person under the influence of the drug may believe himself to be invulnerable to harm and take unwarranted risks, like several of the patients with panic reactions. We are not aware of any reports of prolonged adverse effects that have occurred when

LSD has been used as a psychotherapeutic adjunct. However, it is reasonable to predict that some cases of recurrence of symptoms and appearance of psychosis in previously compensated people will occur as experience with the drug grows. From these patients, who can be followed for a long time, it may be possible to learn more of the physiology associated with recurrence.

The promise of the good to be achieved through the psychedelic experience is reminiscent of the optimism that accompanied the introduction of cocaine and heroin. Initially, only the beneficial effects of these drugs were seen; it took more experience before their undesirable properties were recognized. It is becoming apparent that the indiscriminate use of LSD in the general population has unfortunate sequelae. Although recovery from the panic state appears to be rapid it should be noted that so far there is no information on the possible long-range effects of these intense panic states. At present there is evidence that prolonged psychosis and recurrence of symptoms do appear in a small percentage of an unselected population taking the drug in hope of alleviating anxiety and achieving stability of personality, without any other therapeutic assistance. Because of the widespread use of LSD, we hope that the deleterious effects will be evaluated in juxtaposition to the more optimistic claims of its enthusiasts.

SUMMARY AND CONCLUSIONS

LSD has become increasingly popular among a group of people who are seeking to enrich their artistic and aesthetic awareness and among many who are hoping to increase their self-awareness in a "rational" and rapid fashion without undergoing the stress, work and expense associated with psychotherapy. As a result of indiscriminate, widespread use of the drug, there has been a sudden upsurge in the number of patients admitted to Bellevue Psychiatric Hospital because of adverse reactions.

Three types are described: acute panic reactions; recurrence of symptoms in a period of abstinence after multiple ingestion; and prolonged psychosis. The immediate prognosis in the first group is good, but there are no long-range follow-up results. The patients of the other two groups showed some impairment of performance at the time of our last contact with them.

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INTESTINAL ABSORPTION AND RENAL EXTRACTION OF CYSTINE AND CYSTEINE IN CYSTINURIA*

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A NUMBER of in vivo¹⁻³ and in vitro⁴⁻⁶ studies in cystinuric patients have shown the presence of defects in renal and intestinal transport of the dibasic amino acids lysine, arginine and ornithine. However, studies of intestinal absorption of cystine and the mechanisms by which this amino acid appears in the urine in such marked excess in cystinuria have been far more difficult to interpret. An intestinal-transport defect for cystine has been demonstrated in vitro,^{5,6} and Milne and his co-workers³ have called attention to previous in vivo feeding studies suggesting defective absorption of this amino acid. Several studies⁷⁻⁹ have reported that the renal clearance of cystine approaches that for inulin in homozygous cystinuric patients, suggesting complete failure of renal tubular reabsorption. Other investigators^{10,11} have described cystine clearances in some cases of cystinuria distinctly above those obtained with inulin and, hence, have postulated secretion of this amino acid. Even more puzzling are the results of studies of renal extraction of cystine and cysteine in a single cystinuric subject. Frimpter et al.¹² noted that the renal arteriovenous difference for cystine was unremarkable whereas that for cysteine was very high, and on these grounds suggested that the large quantities of cystine excreted in the urine might result from aberrant cysteine metabolism in the kidney, causing the appearance of the dimer, cystine, in the urine. Finally, Fox and his associates⁴ found no defect for cystine uptake by slices of kidney cortex obtained from cystinuric subjects.

It has previously been reported that cystinuria, as it appears clinically, represents at least three biochemically and genetically distinct diseases.¹³ The present studies were undertaken to determine if we could resolve some of the conflicting findings in the

literature by taking into account the genetic heterogeneity present in patients with cystinuria, and to investigate certain aspects of intestinal and renal metabolism of cystine and cysteine using current techniques that allow separation of these closely related amino acids.¹⁴

METHODS AND MATERIALS

Eleven normal volunteers and 9 patients with documented homozygous cystinuria participated in these studies. The cystinuric subjects are divided into Types 1, 2 and 3 on the basis of the criteria noted in Table 1.¹³ All subjects were admitted to the Clinical Center of the National Institutes of Health for these investigations. None of the control or cystinuric subjects had evidence of active infection, renal insufficiency or other clinical conditions that might have been expected to alter the findings obtained.

Determination of Plasma Cystine and Cysteine

Brigham, Stein and Moore¹⁴ reported that they could prevent oxidation of cysteine to cystine in plasma by alkylating the cysteine with iodoacetic acid under appropriate conditions to form the stable compound S-carboxymethyl cysteine. We have used this technic to separate plasma cysteine from plasma cystine. Through a syringe 9-ml. blood samples were obtained and immediately placed in a 10-ml. volumetric flask containing iodoacetate,|| 100 mg., sodium bicarbonate, 42 mg., and disodium ethylenediaminetetra-acetic acid (EDTA),|| 20 mg., all dissolved in 1 ml. of 0.1-M phosphate buffer, pH 6.8. The samples were then mixed well and spun for fifteen minutes at 2500 rpm to allow separation of the erythrocytes from plasma and to permit the reaction between iodoacetate and cysteine in plasma to take place.¹⁴ Plasma was then decanted, deproteinized with 1 per cent picric acid and prepared for analysis

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